# 4. INTRODUCTION

## 4.1 Investigational Plan

This study proposes to combine Allovectin-7 gene therapy and recombinant IL-2 (rIL-2) protein therapy in a Phase I protocol to assess safety and response in metastatic melanoma patients. This combination approach is intended to stimulate an immune response by expressing HLA-B7 antigen within the tumor, inducing an allogeneic response and potentially restoring some degree of major histocompatibility complex (MHC) class I tumor antigen presentation, while augmenting the immune response to gene-modified tumor cells with systemic administration of low-dose IL-2 and causing expansion of stimulated NK cells, helper T cells and specific cytotoxic T cells.

# 5. BACKGROUND AND RATIONALE

## 5.1 Overview

Human tumors are immunogenic and can induce effective anti-tumor responses (1). Various approaches to immunotherapy, including interferon alpha (IFN-α), interleukin-2 (IL-2) and specific tumor vaccines, induce remissions in patients with a variety of cancers including melanoma, renal cancer and breast cancer (2-4). In these studies, complete or partial remissions have been observed in 10 to 35% of patients.

Gene therapy with gene-modified tumor cell vaccines offers the promise to improve upon these statistics. In animal models, vaccination protocols with gene-modified tumor cells have proven superior to non-modified tumor cells. Cells are transfected or transduced with genes encoding various immunomodulatory proteins including: IL-2, IL-4, IL-7, IL-12, IFN-γ, TNF-α or GM-CSF (5-11). These cells do not grow when implanted into syngeneic mice, and induce protection to subsequent challenge with wild-type tumor cells. However, this protection is often not induced by pre-immunization with wild-type tumor cells. Also, the effect of immunization with gene-modified cells is usually abrogated by antibody to CD8 + cells suggesting the induction of tumor-specific T cell mediated immunity.

In one experiment, G. Nabel and co-workers (University of Michigan) used the insertion of an allogeneic MHC class I antigen into murine tumor cells *in vivo* to induce an allogeneic response against the tumor (12). In the course of the allogeneic response, an immune response was also induced against the tumor-associated antigens of the wild type tumor. Both transfected and non-transfected tumor cells were killed by a cytotoxic T cell response. Survival was prolonged.

This work was then translated into a clinical study. Five HLA-B7 negative patients with metastatic melanoma received intratumoral injections of the HLA-B7 gene in a plasmid

delivered via a cationic lipid vector. The HLA-B7 DNA, mRNA and HLA-B7 protein were detected in injected tumors from 4/5, 4/5, and 5/5 patients, respectively, and one patient had a partial clinical remission (13).